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Report

The Rodent Hippocampus Is Essential for Nonspatial Object Memory

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Summary

Elucidating the role of the rodent hippocampus in object recognition memory is critical for establishing the appropriateness of rodents as models of human memory and for their use in the development of memory disorder treatments. In mammals, spatial memory [1–6] and nonspatial memory [7, 8] depend upon the hippocampus and associated medial temporal lobe (MTL) structures. Although well established in humans [1, 9], the role of the rodent hippocampus in object memory remains highly debated due to conflicting findings across temporary and permanent hippocampal lesion studies [10–22] and evidence that the perirhinal cortex may support object memory [17, 23, 24]. In the current studies, we used intrahippocampal muscimol microinfusions to transiently inactivate the male C57BL/6J mouse hippocampus at distinct stages during the novel object recognition (NOR) task: during object memory encoding and consolidation, just consolidation, and/or retrieval. We also assessed the effect of temporary hippocampal inactivation when objects were presented in different contexts, thus eliminating the spatial or contextual components of the task. Lastly, we assessed extracellular dorsal hippocampal glutamate efflux and firing properties of hippocampal neurons while mice performed the NOR task. Our results reveal a clear and compelling role of the rodent hippocampus in nonspatial object memory.

Results

Mice were surgically implanted with intracranial infusion cannulae or recording electrodes at least 1 week before the onset of behavioral testing. The dorsal hippocampus was bilaterally inactivated at discrete time points relative to the novel object recognition (NOR) task: before the sample session in order to affect encoding and consolidation, after the sample session (consolidation), or before the test session (retrieval) (Figure 1A). During the sample session, each mouse explored two identical objects until the object exploration criterion was reached: 30 s exploration of both objects or 38 s of either object within 10 min, except where otherwise noted. Similar latency to criterion between groups established equal motivation to explore objects. After 24 hr, each mouse was given a 5 min test session with one familiar and one novel object. Preference for exploring the novel object was determined by calculation of a discrimination ratio for each mouse (Discrimination Ratio = T_{novel} -$T_{familiar}$/T_{novel}+$T_{familiar}$). Discrimination ratios were analyzed for treatment differences in object memory. Cannula placements were verified histologically (Figure 1B). All procedures were approved by the FAU Institutional Animal Care and Use Committee.

Experiment 1: The Hippocampus Is Required for Object Memory Encoding and Consolidation

Naive mice received intrahippocampal muscimol or the saline vehicle 20 min before the sample session, ensuring hippocampal inactivation across encoding and into the consolidation stage [25]. Both groups reached sample session exploration criterion in similar times [saline 448 s, muscimol 360 s; $t(11.52) = 1.489$, n.s.] and spent similar total amounts of time exploring test session objects [$t(15) = 1.147$, n.s.]. However, muscimol group discrimination ratios were significantly lower than those of the saline group [$t(15) = 2.47$, $p = 0.026$; Figure 1C], suggesting that inactivation of the hippocampus 20 min prior to the sample session prevents encoding and/or consolidation of object memory.

Experiments 2–4: The Hippocampus Is Required for Object Memory Consolidation

Naive mice received intrahippocampal muscimol or saline immediately after the sample session (experiment 2). Sample session latency to criterion was similar between future treatment groups [saline 469 s, muscimol 459 s; $t(21) = 1.93$, n.s]. However, discrimination ratios of the muscimol group were significantly lower than those of the saline group [$t(21) = 5.93$, $p < 0.001$; Figure 1D]. Another cohort of mice received intrahippocampal anisomycin both immediately and 2 hr after the sample session to disrupt hippocampal protein synthesis during consolidation (experiment 3). Discrimination ratios of the anisomycin-treated mice were also significantly lower than those of the vehicle group [$t(25) = 6.51$, $p < 0.001$, Figure 1E], consistent with a prior report [26]. NOR was spared in mice that received only intrahippocampal anisomycin 2 hr after the sample session (experiment 4; Figure 1E). Interestingly, intrahippocampal anisomycin given 3 hr, but not 6 hr, after the sample session impaired NOR [26]; therefore, the precise dynamics of protein-synthesis-dependent consolidation of object memory remain unclear. Altogether, our results indicate that consolidation of object memory requires a functional hippocampus and hippocampal protein synthesis occurring < 2 hr after the sample session.

Experiment 5: Hippocampal Inactivation during All Memory Stages Impairs NOR Performance

To test our hypothesis that the frequently reported spared NOR after permanent hippocampal lesions is due to compensatory changes within the medial temporal lobe (MTL), we inactivated the hippocampus during encoding, consolidation, *and* retrieval phases. Naive mice received intrahippocampal muscimol or saline 20 min before and 2 hr after the sample

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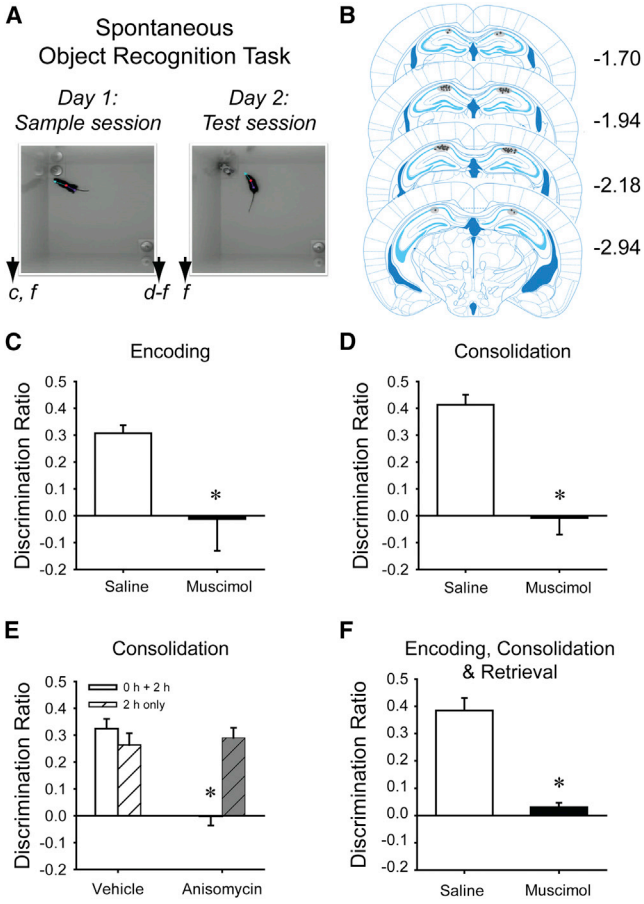

Figure 1. Encoding, Consolidation, and Retrieval of Object Memory by C57BL/6J Mice Requires the Hippocampus; Referring to Experiments 1–5

(A) Depiction of the NOR task sessions. Arrowheads indicate when intrahippocampal infusions were given for specific experiments, designated by lowercase letters corresponding to their respective graphs (before the sample session, *c*; after the sample session, *d* and *e*; before and after the sample session and before the test session, *f*).

(B) The distribution of intrahippocampal infusion sites within the CA1 region of the dorsal hippocampus for all experiments is depicted in gray shading against respective coronal plates from the Franklin & Paxinos atlas [50] (numbers refer to mm from bregma).

(C and D) Intrahippocampal infusion of muscimol before the sample session (saline, n = 8; muscimol, n = 9) (C) or after the sample session (D) (saline, n = 12; muscimol, n = 11) significantly impaired novel object preference (i.e., object memory) during the test session 24 hr later. Mice exhibited similar levels of object exploration during the test session: before-sample-session vehicle 45 s, muscimol 37 s; after-sample-session saline 39 s, muscimol 41 s.

(E) Intrahippocampal anisomycin immediately and 2 hr after the sample session disrupted novel object preference (vehicle, n = 12; anisomycin, n = 15), although test session object exploration was similar: vehicle 45 s, anisomycin 38 s. However, object memory was spared in mice that received intrahippocampal anisomycin only 2 hr after the sample session (vehicle, n = 12; anisomycin, n = 11), and again, object exploration was similar: vehicle 45 s, anisomycin 37 s.

(F) Novel object preference was also impaired in mice given intrahippocampal muscimol infusions before the sample session, after the sample session, *and* before the test session, simulating a permanent hippocampal lesion (saline, n = 8; muscimol, n = 8). Test session object exploration was equivalent between the two groups: saline 40 s, muscimol 48 s.

All plots depict mean ± SEM.

session and 20 min before the test session. Sample session latencies to criterion were equivalent [saline 474 s, muscimol 404 s; $t(14) = 1.13$, *n.s*]; however, discrimination ratios were significantly lower in muscimol-treated mice than in saline-treated mice [$t(8.46) = 7.241$, $p < 0.001$; Figure 1F]. These results suggest that spared object memory in hippocampal-lesioned rodents is most likely supported by compensatory changes.

Experiments 6 and 7: Inactivating the Hippocampus or Changing Context Blocks the Retrieval of a Strong Object Memory

Naive mice received three 10 min sample sessions in the same arena (one per day; Figure 2A, inset) in order to permit the encoding of a strong object memory. Mice received intrahippocampal fluorophore-conjugated muscimol (FCM; Molecular Probes; Figure 2B) or vehicle 20 min before the test session (experiment 6). Groups exhibited similar object exploration across sample sessions (group x session, $F_{2,28} = 1.46$, *n.s.*; see Figure S1A) and in the test session [Figure 2C, inset; $t(14) = -0.09$, *n.s*]; however, the FCM group discrimination ratios were significantly lower than those of the vehicle group [$t(14) = 3.11$, $p = 0.008$, Figure 2C]. Examination of tissue sections revealed that at 30 min after infusion, FCM spread in an approximately 300 μm radius from the estimated center of each infusion, not beyond the CA1 region of the hippocampus (Figure 1B). With the assumption of a spherical distribution at both infusion sites, FCM affected approximately 1% of the entire hippocampal volume [27]. These results indicate that the dorsal hippocampus is critical for the retrieval of object memory and that very limited hippocampal inactivation is sufficient to impair NOR. For determination of the significance of the context to the encoded strong object memory, a second cohort of mice received three 10 min sample sessions in the same arena on the same day (experiment 7; see Figures S1C and S1D) and a test session 24 hr later in a novel arena. Neither pre-test-session intrahippocampal saline-treated nor muscimol-treated mice exhibited a strong preference for exploring the novel object during the test session, and there was no group difference in the discrimination ratio [$t(8) = 0.19$, n.s.; Figure S1E], presumably because rodents explore familiar objects more when they are presented in a novel context [15, 28, 29].

Experiment 8: Retrieval of Object Memory Is Impaired by Hippocampal Inactivation Even When the Memory Was Encoded in Different Contexts

The above findings are consistent with the view that the NOR deficit after lesion of the hippocampus is due to impaired spatial or contextual memory [13, 17] and that successful NOR among controls is supported by conjunctive object-in-place or object-in-context memory. If so, then presenting to-be-remembered objects in a different context each session should eliminate NOR among controls. Naive mice received three 10 min sample sessions (one per day) with the same objects; each session was presented in a novel context (Figures 2D and S1B, contexts A–C). Twenty-four hours later, mice received intrahippocampal muscimol or vehicle 40 min prior to a test session (context D). Vehicle group discrimination ratios were significantly greater than chance [$t(9) = 6.348$, $p < 0.001$], but those of the muscimol group were not [$t(8) = 1.14$, $p > 0.2$]. Mean discrimination ratios were significantly different between the two groups [$t(17) = -3.09$, $p = 0.007$; Figure 2G], yet test session object exploration was similar (Figure 2G, inset). Thus, vehicle-treated mice recognized the familiar object even in a novel context, but muscimol-treated mice did not. These results strongly support the hypothesis that the mouse hippocampus is necessary for the retrieval of object

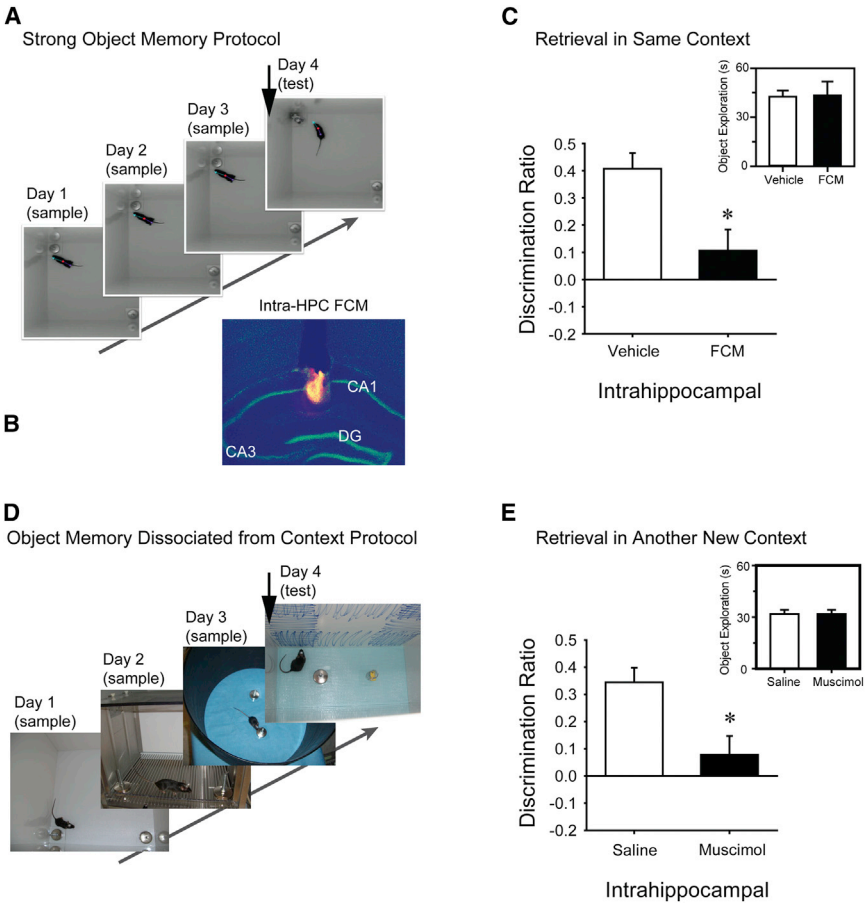

Figure 2. Hippocampal Inactivation Impairs the Retrieval of a Strong Object Memory—Experiment 6—or Object Memory that is Independent of Context—Experiment 8

(A–D) Modified NOR tasks were designed to test the role of the hippocampus in context-dependent (A) and context-independent (D) retrieval of strong object memory. The arrowhead in each montage indicates when the intrahippocampal infusion was conducted. (B) Representative spread of pre-test-session intrahippocampal fluorophore-conjugated muscimol (FCM) within the dorsal hippocampus. (C) Pre-test-session infusion of FCM (experiment 6) impaired object memory in mice that had received three 10 min sample sessions (one per day) in the same context (see photos in A), demonstrating hippocampal involvement in retrieving a strongly encoded object memory (saline, n = 8; FCM, n = 8). (D) Modified NOR task in which mice explored two identical sample objects during three 10 min sample sessions (one per day), each in a distinct context.

(E) Pre-test-session intrahippocampal muscimol impaired the retrieval of object memory during the test session conducted in a novel context, demonstrating hippocampal involvement in retrieving object memory independent of context (saline, n = 9; muscimol, n = 8).

Inset graphs of (C) and (E) depict the test session total object exploration. *p < 0.01 versus the respective vehicle condition. Figures S1A and S1B depict the total object exploration over all sessions as a function of treatment condition for both of these experiments. Figures S1C–S1E depict the results of experiment 7, in which mice received three sample sessions in the same arena (as in experiment 6 above); however, the test session was presented in a novel context.

All plots depict mean ± SEM.

memory even when independent of object-in-place or object-in-context conjunctive memory.

Experiment 9: NOR Task Performance Elevates Extracellular Dorsal Hippocampal Glutamate

For determination of the degree to which this nonspatial task engaged the hippocampus physiologically, glutamate efflux was measured in dialysate samples acquired from the dorsal hippocampus during NOR. Naive mice each received a 10 min sample session in the familiar arena. Twenty-four hours later, mice received an NOR test session or a second sample session (*sample session 2*) during in vivo microdialysis for hippocampal glutamate efflux. The *test session* and *sample session 2* groups of mice exhibited similar latency to sample session criterion [$t(10) = -0.56$, n.s.] and equivalent basal hippocampal glutamate efflux [0.31 ± 0.06 μM and 0.34 ± 0.06 μM; $t(10) = -0.371$, n.s.]. However, glutamate efflux was significantly higher in *the test session mice than in the sample session 2* mice (see Figure 3A; group, $F_{1,10} = 7.12$, p = 0.024; time, $F_{6,\ 60} = 3.65$, p = 0.004; and group × time interaction, $F_{6,\ 60} = 3.39$, p = 0.006). Locomotor activity was equivalent between groups [velocity $t(10) = -0.013$, n.s.; distance traveled, $t(10) = 0.069$, n.s.]. Thus, performance during an NOR test session significantly elevated hippocampal glutamate output.

Experiments 10 and 11: NOR Task Performance Increases Hippocampal CA1 Neuronal Activity

The activity of CA1 pyramidal neurons (experiment 10; n = 23) was stable between two 10 min sample sessions (one per day) in which two identical objects were positioned on opposite ends of a familiar linear track (Figure 3B). A test session was presented 10 min after the second sample session. Overall mean firing rates were significantly greater during the test session (2.52 ± 0.35 Hz) as compared to the second sample session [1.70 ± 0.26 Hz, $t(22) = -4.48$, p < 0.001, Figures 3C and 3D]. Velocity and distance traveled were similar across sessions (p > 0.05). These results provide electrophysiological support for object-recognition-related neuronal activity within the rodent hippocampus.

Hippocampal place cells fire when the rodent occupies a particular location within a given environment [5, 6]. Hippocampal CA1 place cell activity was recorded as mice explored a familiar arena containing a cue card (experiment 11). Place fields were stable in the familiar arena, and the cue card exerted typical stimulus control over the positions of place fields (Figures S2A and S2C, left panel). Next, the same place cells were recorded as mice performed NOR sample and test sessions in the same familiar arena (Figures S2B and S2C, right panel). Firing-rate maps (Figure S2C) indicated that place fields did not remap during the NOR task and that place cell firing rates (Figure S2D) did not change during either the sample or test session [$r = -0.008$, $t(3) = 0.656$, n.s.; Figure S1E]. These results indicate that hippocampal place fields that are already established in a familiar environment are not significantly altered when the mouse subsequently engages in a nonspatial hippocampal-dependent task in that same environment. Together with the observed novelty-induced increase in overall firing rates of CA1 neurons, these findings support prior

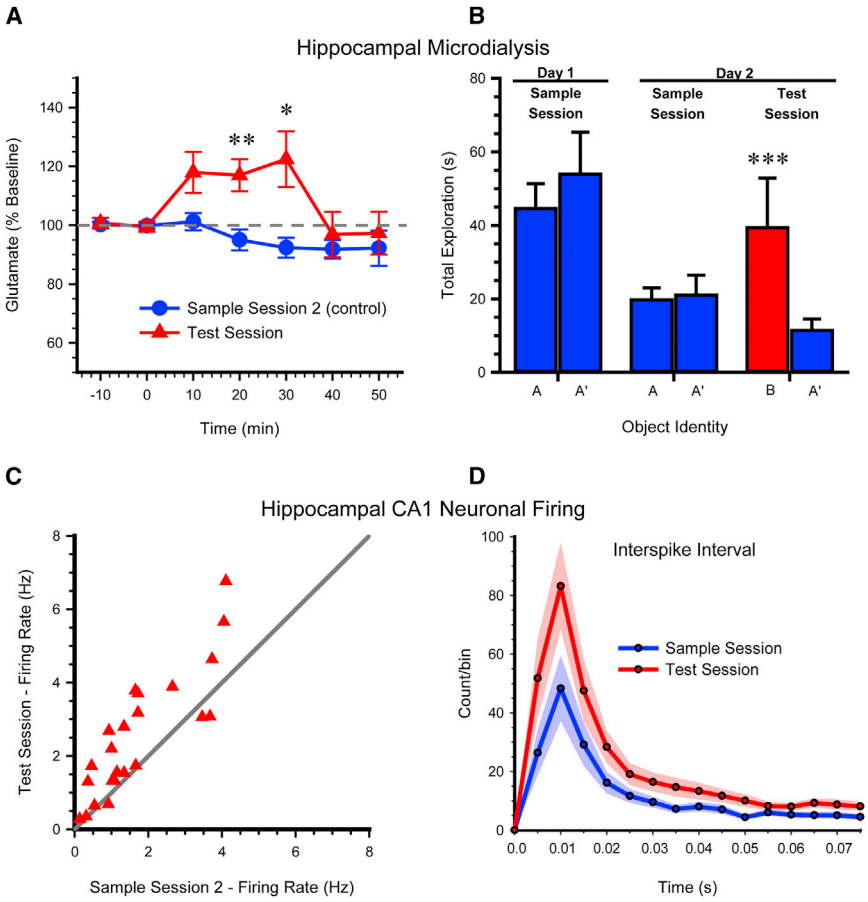

Figure 3. NOR Task Performance Increases Extracellular Glutamate—Experiment 9—and Firing Rates of CA1 Neurons in the Hippocampus—Experiment 10

All mice received a sample session on day 1.

(A) On day 2, microdialysate samples were collected from the hippocampus as mice explored a familiar arena during a baseline period (−10 to 0 min) and then while mice performed either a test session or a second sample session. *p < 0.05, **p < 0.01 versus *sample session 2* group.

(B) Object exploration during respective 10 min recordings of CA1 neuron activity from mice (n = 12) on a linear track on days 1 and 2. ***p < 0.001 indicates successful NOR.

(C) Mean firing rates of 23 simultaneously recorded CA1 pyramidal neurons were significantly greater during the NOR test session as compared to the mean firing rates of the same neurons during the second sample session.

(D) Averaged interspike interval histogram of the 23 CA1 pyramidal neurons during the test session or second sample session. The shaded region shows the SEM for each session average. The plots shown in (A) and (B) depict mean ± SEM. See also Figure S2 for influence of NOR on location-specific firing of CA1 pyramidal neurons.

reports that objects influence CA1 neuronal activity [30, 31] and suggest the presence of CA1 neurons that fire in response to objects independent of location.

Discussion

These behavioral and physiological results establish that the rodent hippocampus is obligatory in object memory, corroborating literature regarding its role in nonspatial memory [9, 32, 33]. Our finding that disruption of approximately 1% of total hippocampal volume blocked object memory processes contradicts reports that permanent lesions of <75% of the hippocampus spare NOR [10, 19]. However, such studies test what a hippocampal-lesioned rodent is capable of remembering (*hippocampal-independent* NOR) rather than whether object memory normally recruits the hippocampus. We argue that traditional lesions provide an adequate model of human amnesia but are ill suited for delineating the hippocampal role in healthy memory processing.

If rats with permanent hippocampal lesions are repeatedly exposed to the same context, then extrahippocampal structures can support contextual memory [34, 35]. Here, object memory encoded over three 10 min sample sessions remained sensitive to pre-test-session hippocampal inactivation, implying that preserved NOR in permanently lesioned rodents is due to compensatory plasticity rather than to normal extrahippocampal capabilities. This view is bolstered by findings of the *hippocampal inactivation during all stages* study, which also confirms that our other findings are not due to state-dependent effects.

It has been argued that the NOR task merely tests conjunctive object-in-place or object-in-context memory, known to be impaired in hippocampal-lesioned rodents [13, 17]. To limit the possibility of place or context aiding object memory retrieval, we presented mice with the objects in four distinct arenas (three sample sessions sample, one test session). If NOR performance is supported by intact spatial or contextual memory, then the control group would have been impaired in this experiment. Alternatively, if nonspatial NOR is supported exclusively by the perirhinal cortex, then intrahippocampal muscimol would not affect performance. We found that saline-treated mice, but not muscimol-treated mice, demonstrated significant novel object preference, indicating that the perirhinal cortex alone cannot support object memory. Thus, the spatial or contextual component of the task is most likely not the primary determinant of whether temporary or permanent hippocampal lesion impairs NOR.

The argument for a double dissociation of the perirhinal cortex and hippocampus posits that memory for objects independent of place or context selectively engages the perirhinal cortex [36], whereas the conjunctive memory for objects in place or context depends on the hippocampus [17, 37]. Thus, *familiarity*, or knowing that an item was recently viewed, depends on the perirhinal cortex, whereas *recollection*, or remembering distinct details about an episode, depends on the hippocampus [38]. This hypothesis predicts that the perirhinal cortex could support NOR performance despite a hippocampal lesion, but we found that NOR performance was impaired after hippocampal inactivation. Evidently, NOR was not supported by perirhinal-dependent familiarity. Our findings substantiate previous reports that hippocampal neurons discharge differentially to novel versus familiar items, item identity, and spatial location [39–41], further weakening the

familiarity/recollection double-dissociation theory. Alternatively, recognition memory may exist on a continuum from weak to strong, whereby the encoding, consolidation, and retrieval of only strong memory (based on familiarity or recollection) is hippocampal dependent [9]. Considering the sensitivity to hippocampal inactivation, the probed memory reported here appears to be a strong one. If a weak counterpart was available in the perirhinal cortex, then it was too weak to influence behavior and was, therefore, negligible.

Evidence supporting the role of the rodent perirhinal cortex in object memory is convincing [17] but does not eliminate a role for the hippocampus. Rather, lesions of perirhinal cortex may disrupt NOR by interfering with the flow of information through the MTL circuit. Unimodal (*what/item*) and polymodal (*where/context*) information streams are routed through perirhinal and parahippocampal cortices, respectively, to the hippocampus [42] and are likely both critical for spatial *and* nonspatial memory functions of the hippocampus. Consistent with this view, perirhinal cortex lesions disrupt the stability of rodent hippocampal place cells [43]. Considering the MTL's dense interconnectedness [9], we propose that the labor of explicit memory is carried by collective participation of the hippocampus, perirhinal cortex, and associated regions but stress that normal object memory processing indeed requires the hippocampus.

We also report physiological evidence that discrimination of novel from familiar objects engages the hippocampus. The significant test session increase in both hippocampal glutamate efflux and mean firing rates of CA1 neurons is consistent with prior reports of novelty-induced increases in hippocampal activity [39, 40] and in vivo recording studies, which indicate that nonspatial events are represented by rodent hippocampal neurons [44]. Whether the increased glutamate efflux observed in mice that received a test session resulted from exposure to a novel object or from object discrimination task performance is unclear. Additional research is needed to elucidate the basis for the increased glutamate efflux during the test session; however, this was beyond the scope of the current study, which aimed to demonstrate that the NOR task activates the hippocampus physiologically. Our finding that NOR test session performance increased CA1 neuron firing rates is consistent with a report that hippocampal neuronal activity represents not only object location but also object identity [31]. Associating specific objects with specific locations [5] can aid in distinguishing one place from another, providing further evidence that the hippocampus supports a global record of experience by maintaining information about the relationships between specific objects encountered in distinct locations.

Although numerous reports state that the hippocampus is not involved in NOR, several studies support our findings [14, 18–20, 22, 45]. Our results elaborate on the conclusions of these supporting studies by establishing the critical and independent contribution of dorsal hippocampal neural activity to discrete stages of object memory, even when that memory is devoid of contextual components. Furthermore, the finding that the rodent hippocampus is involved in NOR is compatible with prior studies of other species, such as those assessing visual recognition memory in primates [46–49]. Considering the known role of the human and nonhuman primate hippocampus in recognition memory, it is likely that the rodent hippocampus plays a similar role. Our findings support this conclusion: the rodent hippocampus isn't just for space anymore.

Supplemental Information

Supplemental Information includes detailed author contributions, Supplemental Experimental Procedures, and two figures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.07.002.

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